

The Response

Applicants are required under 35 USC §121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Upon the allowance of a generic claim, Applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR §1.141.

The Examiner states that the application contains claims directed to the following patentably distinct species of the claimed invention:

Species 1: Formula I, classified in class 514, subclass 47.

Species 2: Formula Ia, classified in class 514, subclass 49.

In Response to the election requirement, Applicants are making the following election. Applicants hereby elect Species 1, Formula I, which includes Formula Ia and Ib. If, and only if, the Examiner further requires Applicants to elect between Formulas Ia and Ib, Applicants will elect Formula Ib.

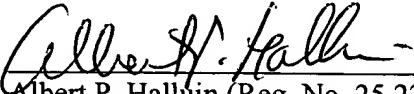
Claims 1-34 are readable upon the elected species.

CONCLUSION

Applicant believes that the application is in good and proper condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 463-8109.

Respectfully submitted,

Date: November 1, 2002


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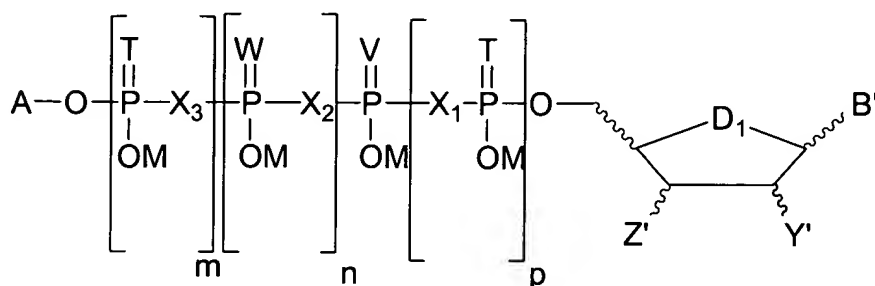
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MARKED-UP VERSION SHOWING CHANGES MADE TO CLAIMS

1. {Amended} [The] A compound [comprising] of general formula I, or salts thereof:

Formula I



wherein:

X₁, X₂, and X₃ are independently selected from the group consisting of [independently or together] oxygen, methylene, monochloromethylene, dichloromethylene, monofluoromethylene, difluoromethylene, and imido;

T, W, and V are independently [or together] oxygen or sulfur;

m= 0, 1 or 2;

n= 0, 1, or 2;

p= 0, 1, or 2 ;

M= H or a pharmaceutically-acceptable inorganic or organic counterion;

D₁ =O or C;

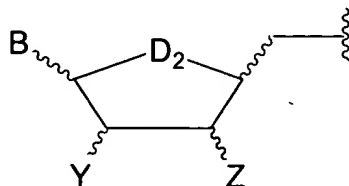
B' is a purine or a pyrimidine residue according to general formulas IV and V which is linked to the 5' position of the furanose or carbocycle via the 9- or 1- position, respectively;

Y' =H or OR₁;

Z' =H or OR₂;

A is elected from the group consisting of M, alkyl, cycloalkyl, aralkyl, aryl, and acylthioalkyl, with or without substituents or heteroatoms; or

A is a nucleoside residue which is defined as:



and which is linked to the phosphate chain via the 5' position of the furanose or carbocycle;

wherein:

Z =H or OR₃;

Y =H or OR₄;

D₂ =O or C;

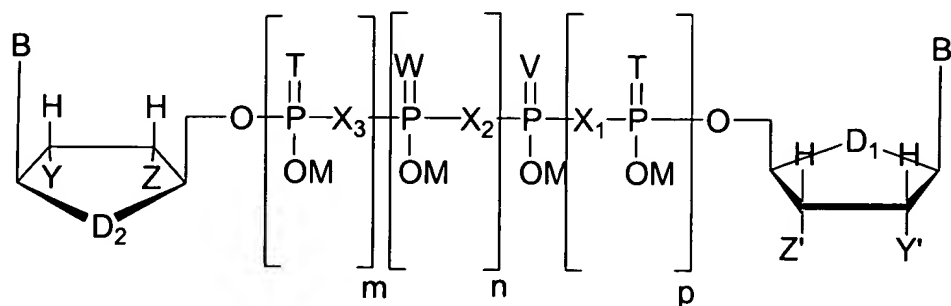
B is a purine or a pyrimidine residue according to general formulas IV and V which is linked to the sugar or carbocycle via the 9- or 1- position, respectively;

R₁, R₂, R₃, and R₄ are H, provided that at least one of the four is a residue according to general [formulas] formula II [and] or III, which is linked to the 2' or 3' furanose or carbocycle hydroxyl oxygen via a carbon atom;

wherein [further provisions are that] when D₁ and D₂ are oxygen, the furanose is [preferably] in the β-configuration; [most preferably in the β-D-configuration;]

wherein [preferred] compounds of general Formula I are molecules whose structures fall within the definitions of Formula Ia [and] or Formula Ib:

Formula Ia



wherein:

X_1 , X_2 , and $X_3=O$;

T, V, and W= O;

M= H, NH_4^+ , Na^+ or other pharmaceutically-acceptable inorganic or organic counterion;

Y' = H, OH, or OR_1 , where R_1 falls under the definition of general formula II;

Z' = OH or OR_2 , where R_2 falls under the definition of general formula II;

Z= OH or OR_3 , where R_3 falls under the definition of general formula II;

Y= H, OH, or OR_4 , where R_4 falls under the definition of general formula II;

$D_1=O$;

$D_2=O$ or C;

B and B' are purine or pyrimidine residues according to general formulas IV and V;

m and p= 0, 1 or 2;

n= 0 or 1;

such that the sum of m+n+p is from 1 to 5; or

X_1 , X_2 , and $X_3=O$;

T, V, and W= O;

M= H, $[NH_4]$ NH_4^+ , Na^+ or other pharmaceutically-acceptable inorganic or organic counterion ;

Y' = H, OH, or OR_1 , where R_1 falls under the definition of general formula III;

Z' = OH or OR_2 , where R_2 falls under the definition of general formula III;

Z= OH or OR_3 , where R_3 falls under the definition of general formula III;

Y= H, OH, or OR_4 , where R_4 falls under the definition of general formula III;

$D_1=O$;

$D_2=O$ or C;

B and B' are purine or pyrimidine residues according to general formulas IV and V;

m and p= 0, 1 or 2;

n= 0 or 1;

such that the sum of m+n+p is from 1 to 5; or

X_1 and $X_3=O$;

X_2 is selected from the group consisting of methylene, monochloromethylene, dichloromethylene, monofluoromethylene, difluoromethylene, and imido;

T, V, and W= O;

M= H, $[NH_4]^+$, Na^+ or other pharmaceutically-acceptable inorganic or organic counterion ;

$Y'=H$, OH, or OR_1 , where R_1 falls under the definition of general formula II;

$Z'=OH$ or OR_2 , where R_2 falls under the definition of general formula II;

$Z=OH$ or OR_3 , where R_3 falls under the definition of general formula II;

$Y=H$, OH, or OR_4 , where R_4 falls under the definition of general formula II;

$D_1=O$;

$D_2=O$ or C;

B and B' are purine or pyrimidine residues according to general formulas IV and V;

m and p= 0, 1 or 2;

n= 1;

such that the sum of m+n+p is from 1 to 5; or

X_1 and $X_3=O$;

X_2 is selected from the group consisting of methylene, monochloromethylene, dichloromethylene, monofluoromethylene, difluoromethylene, and imido;

T, V, and W= O;

M= H, $[NH_4]^+$, Na^+ or other pharmaceutically-acceptable inorganic or organic counterion;

$Y'=H$, OH, or OR_1 , where R_1 falls under the definition of general formula III;

$Z'=OH$ or OR_2 , where R_2 falls under the definition of general formula III;

$Z=OH$ or OR_3 , where R_3 falls under the definition of general formula III;

$Y=H$, OH, or OR_4 , where R_4 falls under the definition of general formula III;

$D_1=O$;

D_2 is O or C;

B and B' are purine or pyrimidine residues according to general formulas IV and V;

m and p= 0,1 or 2;

$n=1$;

such that the sum of $m+n+p$ is from 1 to 5; or

X_1 and $X_3=O$;

X_2 is selected from the group consisting of methylene, monochloromethylene, dichloromethylene, monofluoromethylene, difluoromethylene, and imido;

$T=S$;

V and $W=O$;

$M=H$, $[NH_4] NH_4^+$, Na^+ or other pharmaceutically-acceptable inorganic or organic counterion;

$Y'=H$, OH , or OR_1 , where R_1 falls under the definition of general formula II;

$Z'=OH$ or OR_2 , where R_2 falls under the definition of general formula II;

$Z=OH$ or OR_3 , where R_3 falls under the definition of general formula II;

$Y=H$, OH , or OR_4 , where R_4 falls under the definition of general formula II;

$D_1=O$;

$D_2=O$ or C ;

B and B' are purine or pyrimidine residues according to general formulas IV and V;

m , n , and $p=1$; or

X_1 and $X_3=O$;

X_2 is selected from the group consisting of methylene, monochloromethylene, dichloromethylene, monofluoromethylene, difluoromethylene, and imido;

$T=S$;

V and $W=O$;

M is selected from the group consisting of H , $[NH_4] NH_4^+$, Na^+ and other pharmaceutically-acceptable inorganic or organic counterion;

$Y'=H$, OH , or OR_1 , where R_1 falls under the definition of general formula III;

$Z'=OH$ or OR_2 , where R_2 falls under the definition of general formula III;

$Z=OH$ or OR_3 , where R_3 falls under the definition of general formula III;

$Y=H$, OH , or OR_4 , where R_4 falls under the definition of general formula III;

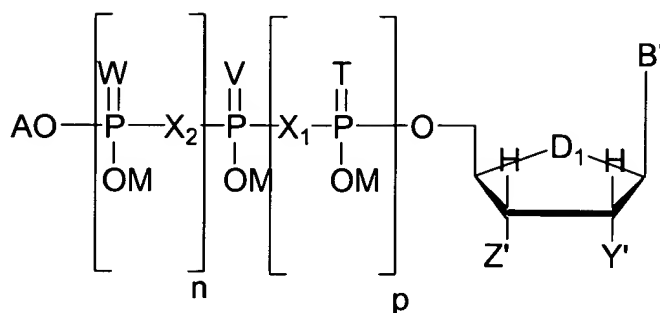
$D_1=O$;

$D_2 = O$ or C ;

B and B' are purine or pyrimidine residues according to general formulas IV and V;

m , n , and $p = 1$; [or]

Formula Ib



[where for general formula I, $m=0$, and all other definitions remain the same;]

wherein:

A is elected from the group consisting of M , alkyl, cycloalkyl, aralkyl, aryl, and acylthioalkyl, with or without substituents or heteroatoms;

X_1 and $X_2 = O$;

T , V , and $W = O$;

$M = H$, $[NH_4] NH_4^+$, Na or other pharmaceutically-acceptable inorganic or organic counterion;

$Y' = H$, OH , or OR_1 , where R_1 falls under the definition of general formula II;

$Z' = H$, OH or OR_2 , where R_2 falls under the definition of general formula II;

[With] with the provision that at least one of Y' and Z' is OR_1 or OR_2 ;

$D_1 = O$ or C ;

B' is purine or pyrimidine residue according to general formulas IV and V;

n and p are 0, 1, or 2 such that the sum of $n+p$ is from 1 to 3; or

A is selected from the group consisting of M , alkyl, cycloalkyl, aralkyl, aryl, and acylthioalkyl, with or without substituents or heteroatoms;

X_1 and $X_2 = O$;

T, V, and W = O;

M is selected from the group consisting of H, $[NH_4] \underline{NH_4}^+$, Na and other pharmaceutically-acceptable inorganic or organic counterion;

$Y' = OR_1$, where R_1 falls under the definition of general formula III;

$Z' = OR_2$, where R_2 falls under the definition of general formula III;

$D_1 = O$ or C;

B' is purine or pyrimidine residue according to general formulas IV and V;

n and p are 0, 1, or 2 such that the sum of n+p is from 1 to 3; or

A is selected from the group consisting of M, alkyl, cycloalkyl, aralkyl, aryl, and acylthioalkyl, with or without substituents or heteroatoms;

X_1 and $X_2 = O$;

T and V = O;

W = S;

M = H, $[NH_4] \underline{NH_4}^+$, Na or other pharmaceutically-acceptable inorganic or organic counterion;

$Y' = H, OH$, or OR_1 , where R_1 falls under the definition of general formula II;

$Z' = H, OH$ or OR_2 , where R_2 falls under the definition of general formula II;

[With] with the provision that at least one of Y' and Z' is OR_1 or OR_2 ;

$D_1 = O$ or C;

B' is purine or pyrimidine residue according to general formulas IV and V;

p is 0, 1, or 2 such that the sum of n+p is from 1 to 3;

n=1; or

A is selected from the group consisting of M, alkyl, cycloalkyl, aralkyl, aryl, and acylthioalkyl, with or without substituents or heteroatoms;

X_1 and $X_2 = O$;

T and V = O;

W = S;

M is selected from the group consisting of H, [NH₄] NH_4^+ , Na and other pharmaceutically-acceptable inorganic or organic counterion;

Y' = OR₁, where R₁ falls under the definition of general formula III;

Z' = OR₂, where R₂ falls under the definition of general formula III;

D₁ = O or C;

B' is purine or pyrimidine residue according to general formulas IV and V;

p is 0, 1, or 2 such that the sum of n+p is from 1 to 3;

n=1; or

A is selected from the group consisting of M, alkyl, cycloalkyl, aralkyl, aryl, and acylthioalkyl, with or without substituents or heteroatoms;

X₁ = O;

[X₂ is] X₂ is selected from the group consisting of methylene, monochloromethylene, dichloromethylene, monofluoromethylene, difluoromethylene, and imido;

T, V, and W = O;

M is selected from the group consisting of H, [NH₄] NH_4^+ , Na and other pharmaceutically-acceptable inorganic or organic counterion;

Y' = H, OH, or OR₁, where R₁ falls under the definition of general formula II;

Z' = H, OH or OR₂, where R₂ falls under the definition of general formula II;

[With] with the provision that at least one of Y' and Z' is OR₁ or OR₂;

D₁ = O or C;

B' is purine or pyrimidine residue according to general formulas IV and V;

p is 0, 1, or 2 such that the sum of n+p is from 1 to 3;

n=1; or

A is selected from the group consisting of M, alkyl, cycloalkyl, aralkyl, aryl, and acylthioalkyl, with or without substituents or heteroatoms;

X₁ = O;

[X₂ is] X₂ is selected from the group consisting of methylene, monochloromethylene, dichloromethylene, monofluoromethylene, difluoromethylene, and imido;

T, V, and W = O;

M is selected from the group consisting of H, [NH₄] NH₄⁺, Na and other pharmaceutically-acceptable inorganic or organic counterion;

Y' = H, OH, or OR₁, where R₁ falls under the definition of general formula III;

Z' = H, OH or OR₂, where R₂ falls under the definition of general formula III;

D₁ = O or C;

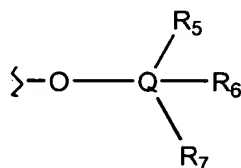
B' is purine or pyrimidine residue according to general formulas IV and V;

p is 0, 1, or 2 such that the sum of n+p is from 1 to 3;

n=1;

wherein, for compounds according to Formula Ia or Ib, where Y' = OR₁, Z' = OR₂, Z = OR₃ and/or Y = OR₄, at least one of the four [must be] is a residue which is linked directly to the corresponding 2' or 3' hydroxyl oxygen of the furanose or carbocycle via a carbon atom; [and for the most part, this] wherein said residue falls within the scope of formula II or formula III:

Formula II



wherein:

O is the corresponding 2' or 3' oxygen of the furanose or carbocycle;

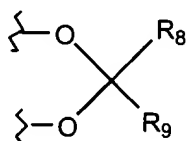
R₅, R₆, and R₇ are selected from the group consisting of H, an alkyl, cycloalkyl, aralkyl, aryl, substituted aralkyl, and substituted aryl, such that the moiety defined according to formula II is an ether; or

[provided that] R₅ and R₆ are taken together to [mean] be oxygen or sulfur doubly bonded to Q, and R₇ is selected from the group consisting of alkyl, cycloalkyl, aralkyl, aryl, substituted aralkyl, and substituted aryl, such that the moiety defined according to formula II is an ester or thioester; or

[provided that] R₅ and R₆ are taken together to [mean] be oxygen or sulfur doubly bonded to Q, and R₇ is amino or mono- or disubstituted amino, where the substituents are selected from the group consisting of alkyl, cycloalkyl, aralkyl, aryl, substituted aralkyl,

and substituted aryl, such that the moiety according to formula II is a carbamate or thiocarbamate; or
[provided that] R₅ and R₆ are taken together to [mean] be oxygen or sulfur doubly bonded to Q, and R₇ is selected from the group consisting of alkoxy, cycloalkoxy, aralkyloxy, aryloxy, substituted aralkyloxy, and substituted aryloxy, such that the moiety according to formula II is a carbonate or thiocarbonate; or
[provided that] R₅ and R₆ are taken together to [mean] be oxygen or sulfur doubly bonded to Q and both the 2' and 3' oxygens of the furanose are directly bound to Q to form a cyclical carbonate or thiocarbonate, R₇ is not present; [or]

Formula III

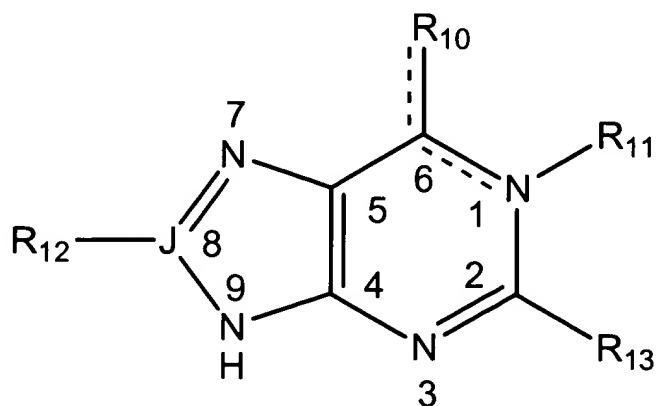


wherein:

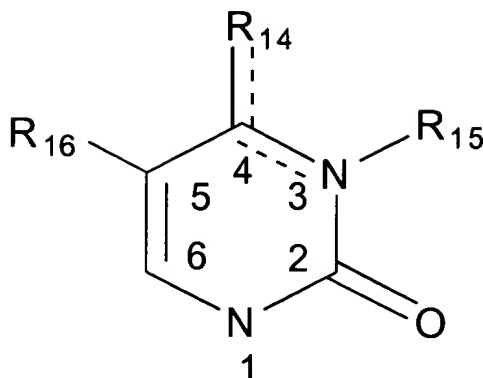
O is the 2' and 3' oxygens of the furanose or carbocycle; and
the 2' and 3' oxygens of the furanose or carbocycle are linked by a common carbon atom to form a cyclical acetal, cyclical ketal, or cyclical orthoester; and
for cyclical acetals and ketals, R₈ and R₉ are independently selected from the group consisting of [independently] hydrogen, alkyl, cycloalkyl, aralkyl, aryl, substituted aralkyl, and substituted aryl; or [may be] are joined together to form a homocyclic or heterocyclic ring composed of 3 to 8 atoms, or
for cyclical orthoesters, R₈ is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aralkyl, aryl, substituted aralkyl, and substituted aryl,
and [R₉] R₉ is selected from the group consisting of alkyloxy, cycloalkyloxy, aralkyloxy, aryloxy, substituted aralkyloxy, and substituted aryloxy;
[wherein, in general, R₅ to R₉ are selected from the group consisting of, but are not limited to, the following:

- a) alkyl groups are from 1 to 8 carbons, either straight chained or branched, with or without unsaturation and with or without heteroatoms;
- b) cycloalkyl groups are from 3 to 8 carbons, with or without unsaturation, and with or without heteroatoms;
- c) aralkyl groups are from 1 to 5 carbons in the alkyl portion, and are monocyclic or polycyclic moieties from 4 to 8 carbons per ring, with or without heteroatoms, in the aryl portion;
- d) aryl groups are monocyclic or polycyclic moieties from 4 to 8 carbons, with or without heteroatoms; and
- these groups may or may not bear substituents; or
- wherein preferred substituents on the foregoing groups are selected from the group consisting of, but are not limited to, hydroxy, nitro, methoxy, fluoro, chloro, bromo, iodo, methyl, ethyl, propyl, butyl, thioalkyl, alkoxy, carboxyl, cyano, amino, substituted amino, trifluoromethyl, phenyl, cyclopropyl, cyclopentyl, and cyclohexyl; and
- wherein preferred heteroatoms are selected from the group consisting of oxygen, nitrogen, and sulfur;]
- B and B' are independently a purine residue, as in formula IV, linked through the 9-position, or a pyrimidine residue, as in formula V, linked through the 1-position;
- wherein, provided when D₁ and D₂ are oxygen, the ribosyl moieties are in the [preferred] D- configuration[, but may be L-, or D- and L-];

Formula IV



Formula V



wherein:

R₁₀ and R₁₄ are selected from the group consisting of hydroxy, oxo, amino, mercapto, alkylthio, alkyloxy, aryloxy, alkylamino, cycloalkylamino, aralkylamino, arylamino, diaralkylamino, diarylamino, or dialkylamino, where the alkyl groups are optionally linked to form a heterocycle; or

R₁₀ and R₁₄ are acylamino according to Formula VI, provided that they incorporate an amino residue from the C-6 position of the purine or the C-4 position of the pyrimidine; or

when R₁₀ in a purine or R₁₄ in a pyrimidine has as its first atom nitrogen, R₁₀ and R₁₁ or R₁₄ and R₁₅ are taken together to form a 5-membered fused imidazole ring, optionally substituted on the etheno ring with R₅-R₉ selected from the group consisting of alkyl, cycloalkyl, aralkyl, or aryl moieties, as described above;

J is carbon or nitrogen, with the provision that when nitrogen, R₁₂ is not present;

R₁₁ is hydrogen, O or is absent;

R₁₂ is selected from the group consisting of hydrogen, alkyl, azido, alkylamino, arylamino, aralkylamino, alkoxy, aryloxy, aralkyloxy, alkylthio, arylthio, aralkylthio, and ω -A(C₁₋₆alkyl)B- wherein A and B are selected from the group consisting of independently amino, mercapto, hydroxy and carboxyl;

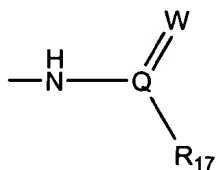
R₁₃ is selected from the group consisting of hydrogen, chlorine, amino, monosubstituted amino, disubstituted amino, alkylthio, arylthio, and aralkylthio, where the substituent on sulfur contains up to a maximum of 20 carbon atoms, with or without unsaturation;

R₁₅ is selected from the group consisting of hydrogen, and acyl, such as acetyl, benzoyl, phenylacetyl, with or without substituents;

R₁₆ is selected from the group consisting of hydrogen, methyl, alkyl, halo, alkyl, alkenyl, substituted alkenyl, alkynyl, and substituted alkynyl;

[wherein compounds where R₁₀ or R₁₄ is acylamino fall within the scope of formula VI:]

Formula VI



wherein:

NH is the amino residue at the C-6 position in a purine or the amino residue at the C-4 position in a pyrimidine;

Q is a carbon atom;

W is oxygen or sulfur;

R₁₇ is amino or mono- or disubstituted amino such that the moiety according to formula VI is a urea or thiourea; or

R₁₇ is selected from the group consisting of alkoxy, aralkyloxy, aryloxy, substituted aralkyloxy, and substituted aryloxy, such that the moiety according to formula VI is a carbamate or thiocarbamate; or

R₁₇ is selected from the group consisting of alkyl, cycloalkyl, aralkyl, and aryl, with or without substituents or heteroatoms, such that the moiety according to formula VI is an amide.

16. (Amended) The method according to Claim 3, wherein said diseases or conditions associated with platelet aggregation are disorders or procedures characterized by thrombosis, primary arterial thrombotic complications of atherosclerotic disease, thrombotic complications of interventions of atherosclerotic disease, thrombotic complications of surgical or mechanical damage, mechanically – induced platelet activation, shunt occlusion, thrombosis secondary to vascular damage and inflammation, indications with a diffuse thrombotic/platelet consumption component, venous thrombosis, coronary arterial thrombosis, pathological effects of atherosclerosis and arteriosclerosis, platelet aggregation and clot formation in blood and blood products during storage, chronic or acute states of hyper-aggregability, reocclusion of an artery or vein following fibrinolytic therapy, platelet adhesion associated with extracorporeal circulation, thrombotic complications associated with thrombolytic therapy, thrombotic complications associated with coronary and other angioplasty, [and] or thrombotic complications associated with coronary artery bypass procedures.

17. (Amended) The method according to Claim 16, wherein said disorders or procedures [associated] characterized with thrombosis are unstable angina, coronary angioplasty, [and] or myocardial infarction.

18. (Amended) The method according to Claim 16, wherein said primary arterial thrombotic complications of atherosclerosis are thrombotic stroke, peripheral vascular disease, [and] or myocardial infarction without thrombolysis.

19. (Amended) The method according to Claim 16, wherein said thrombotic complications of interventions of atherosclerotic disease are angioplasty, endarterectomy, stent placement, coronary [and] or other vascular graft surgery.

20. (Amended) The method according to Claim 16, wherein said thrombotic complications of surgical or mechanical damage are tissue salvage following surgical or accidental trauma, reconstructive surgery including skin flaps, [and “reductive”] or reductive surgery such as breast reduction.
21. (Amended) The method according to Claim 16, wherein said mechanically – induced platelet activation is caused by cardiopulmonary bypass resulting in microthromboembolism [and] or storage of blood products.
22. (Amended) The method according to Claim 16, wherein said shunt occlusion is renal dialysis [and] or plasmapheresis.
23. (Amended) The method according to Claim 16, wherein said [thromboses] thrombosis secondary to vascular damage and inflammation [are] is vasculitis, arteritis, glomerulonephritis [and] or organ graft rejection.
24. (Amended) The method according to Claim 16, wherein said indications with a diffuse thrombotic/platelet consumption component are disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, heparin-induced thrombocytopenia, [and] or pre-eclampsia/eclampsia.
25. (Amended) The method according to Claim 16, wherein said venous thrombosis [are] is deep vein thrombosis, veno-occlusive disease, hematological conditions, [and] or migraine.
26. (Amended) The method according to Claim 25, wherein said hematological conditions are thrombocythemia [and] or polycythemia.

27. (Amended) The method according to Claim 16, wherein said coronary arterial thrombosis is associated with unstable angina, coronary angioplasty [and] or acute myocardial infarction.

28. (Amended) The method according to Claim 16, wherein pathological effects of atherosclerosis and arteriosclerosis are arteriosclerosis, acute myocardial infarction, chronic stable angina, unstable angina, transient ischemic attacks, [and] strokes, peripheral vascular disease, arterial thrombosis, preeclampsia, embolism, restenosis or abrupt closure following angioplasty, carotid endarterectomy, [and] or anastomosis of vascular grafts.

29. (Amended) The method according to Claim 16, wherein said chronic or acute states of hyper-aggregability is caused by DIC, septicemia, surgical or infectious shock, post-operative and post-partum trauma, cardiopulmonary bypass surgery, incompatible blood transfusion, abruptio placenta, thrombotic thrombocytopenic purpura, snake venom [and] or immune diseases.

31. (Amended) The method according to Claim 30, wherein said fibrinolytic agent is selected from [a] the group consisting of natural or synthetic products which directly or indirectly cause lysis of a the fibrin clot.

32. (Amended) The method according to Claim 30, wherein said fibrinolytic agent is a plasminogen activator selected from [a] the group consisting of anistreplase, urokinase [(UK)], pro-urokinase [(PUK)], streptokinase [(SK)], tissue plasminogen activator [(tPA)] and mutants[,], or variants thereof, which retain plasminogen activator activity.

33. (Amended) The method according to Claim 32, wherein said variants are selected from [a] the group consisting of variants which have been chemically modified, variants which one or more amino acids have been added, deleted or substituted [or] and variants with one or more modified functional domains.

34. (Amended) The method according to Claim 33, wherein said modified functional domains are added, deleted or altered by combining the active site of one plasminogen activator or fibrin binding domain [of] with another plasminogen activator or fibrin binding molecule.